

Commonly encountered central nervous system infection in the neurointensive care unit

Sophia De Saram

Abstract

A wide variety of community- and hospital-associated infections of the central nervous system (CNS) may be encountered on the neurointensive care unit (NICU). Distinguishing between the potential infectious aetiologies and differentiating from non-infectious causes can be challenging. Specific elements of the history and establishing early the immune status and travel history of an individual with possible infection can guide targeted additional testing. Increasing prevalence of iatrogenic immunosuppression means that familiar pathogens can present atypically. In addition, epidemiology of pathogens is changing with rising antimicrobial resistance and autochthonous cases of previously travel-associated pathogens.

Keywords Abscess; encephalitis; infection; meningitis; neurointensive care; ventriculitis

Acute community-acquired bacterial meningitis

While the epidemiology of community-acquired bacterial meningitis has changed over recent decades, largely due to vaccination programmes, the rate of bacterial meningitis in adults remains relatively unchanged and mortality is still about 20%.

The most common pathogens in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*.

Clinical features

About 95% of patients have at least two of the following: fever, headache, neck stiffness, altered mental status. Preceding ear infection or mastoiditis suggests *S. pneumoniae* as the likely cause. Pneumococcal meningitis is associated with higher incidence of seizures, focal neurological defect and coma. When rash is present the causative organisms is *N. meningitidis* in 92% of cases, however rash is absent in more than a third of *N. meningitidis* meningitis cases.

Investigations

Blood cultures and lumbar puncture (LP) (for those without clinical contraindications) should be performed within 1 hour of admission. Imaging prior to lumbar puncture is only recommended if clinical features of raised intra-cranial pressure are present. For suggested initial investigations see [Table 1](#).

Sophia De Saram FRCPATH MRCP DTM&H is a Consultant Microbiologist and Infectious Diseases Physician at the National Hospital for Neurology and Neurosurgery and University College London Hospitals, UK. Conflicts of interest: none declared.

Learning objectives

After reading this article, you should be able to:

- recognize common infections encountered on the neurointensive care unit
- identify the most useful diagnostic tests for patients with neurological and neurosurgical infections
- select the most appropriate antimicrobial agent for common infections

Treatment

Antibiotics should be administered within 1 hour of arrival at hospital, immediately after blood cultures and LP. If LP is delayed, antibiotics should be given, and LP performed as soon as possible after. Empirical treatment is intravenous ceftriaxone 2 g 12-hourly or cefotaxime 2 g 6-hourly. If the patient has travelled in the last 6 months to a country with higher rates of pneumococcal resistance, addition of intravenous (IV) vancomycin or rifampicin should be discussed with local infection specialists. In those over 60 years of age or immunocompromised, amoxicillin 2 g 4-hourly should be added to cover *Listeria*. If the patient has a confirmed history of anaphylaxis to penicillin, then an alternative is chloramphenicol 25 mg/kg 6-hourly (with high-dose IV co-trimoxazole if *Listeria* cover is required).

Adjuvant steroids in high-resource settings reduces mortality and hearing loss, particularly in those with pneumococcal meningitis. UK guidelines therefore advise concomitant dexamethasone 10 mg 6-hourly to be started with antibacterials.

Meningitis associated with surgery or head trauma

A key challenge in this context is distinguishing infective meningitis from aseptic (chemical) meningitis. The main risk factors for infective meningitis are cerebrospinal fluid (CSF) leak, procedures through contaminated sites, e.g. paranasal sinus, trauma resulting in dural breach and concomitant superficial wound infection.

The pathogens involved after sinus surgery or base of skull fracture are predominantly colonisers of the nasopharynx, including *S. pneumoniae* and *H. influenzae*. However, a significant proportion are caused by other colonisers and microbes introduced from the environment, including coagulase negative staphylococci, *Cutibacterium acnes*, *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* spp and yeasts such as *Candida*.

Clinical features

Headache, fever, altered mental status, new seizures and meningism should raise the suspicion of hospital associated meningitis. However, these symptoms are not specific for infective meningitis in this setting as they can also be found in chemical meningitis or may be triggered by infection from another source.²

Investigations

CSF sampling is crucial. After cranial trauma or neurosurgery many patients will have abnormal CSF parameters. The most reliable test for distinguishing infective meningitis from a

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Suggested initial investigations in community-acquired meningitis (adapted from UK meningitis guideline¹)

Sample	Tests
Blood	FBC, U&E, LFTs, CRP, clotting, lactate Blood culture Whole blood for pneumococcal and meningococcal PCR Serum save (for retrospective testing if no cause identified with first line tests)
CSF	Opening pressure Microscopy, culture and sensitivity Protein Lactate and glucose (sent in fluoride blood bottle with paired serum sample for glucose) Viral PCR (HSV1/2, VZV, enterovirus as minimum) Cryptococcal antigen if immunosuppressed CSF save for additional tests, e.g. molecular bacterial tests
Swabs	Bacterial throat swab for meningococcal culture Viral throat swab and stool for enterovirus PCR Viral swab of vesicle for HSV, VZV and enterovirus if vesicles present

CRP, C-reactive protein; CSF, cerebrospinal fluid; FBC, full blood count; HSV, herpes simplex virus; LFT, liver function tests; PCR, polymerase chain reaction; U&E, urea and electrolytes; VZV, varicella-zoster virus.

Table 1

chemical meningitis is CSF culture. Post-surgical and device-associated CSF should undergo prolonged culture to allow slower growing pathogens, e.g. anaerobes, to be detected. In those who have received prior antibiotics bacterial 16S polymerase chain reaction (PCR) can be helpful.

Treatment

Empirical antibiotic therapy is usually a third-generation cephalosporin or meropenem but should be guided by local resistance patterns and previous microbiology results in discussion with local infection specialists.

CSF shunt-associated infections and ventriculitis

CSF shunts may be temporary external shunts, e.g. extra-ventricular drains (EVD) and lumbar drains (LD) or permanent internal shunts, predominantly ventriculo-peritoneal (VP), ventriculo-pleural (VPI) and ventriculo-atrial (VA). Whilst CSF shunt-related infections can present on a continuum with hospital-associated meningitis, in many cases the aetiological agents and clinical features differ significantly.

The pathogens causing shunt infections vary depending on the setting. In most UK centres the common pathogens are coagulase negative staphylococci, *S. aureus* and *C. acnes* but a significant proportion are caused by Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* spp and, more rarely, *Enterococcus* spp. and yeasts such as *Candida*.

External shunt infection rates are between 0% and 22%, depending on definition, setting and patient population.

Factors associated with EVD infection and practices that contribute to reduced risk

Increased risk	Best practice
Frequent manipulation of catheter Irrigation of catheter	Standardized protocols for insertion Adherence to aseptic technique at insertion
CSF leakage from insertion site Intraventricular or subarachnoid haemorrhage Manipulations/reinsertions due to malfunction	Pre-EVD insertion use of single dose prophylactic antibiotic Use of antimicrobial-impregnated catheters Limit manipulation/avoid fixed interval exchange of EVDs Avoid routine sampling of CSF Avoid prolonged prophylactic antibiotics for EVD duration Timely removal of catheter
CSF, cerebrospinal fluid; EVD, extra-ventricular drain.	

Table 2

Internalised shunt infection rates are usually between 4% and 17%. See Table 2 for factors that influence EVD infection rates.

Clinical features

The clinical features associated with external shunt infections are altered mental status, headache, fever. Meningism is rare. Diagnosing infected external shunts in the setting of intracranial bleed is particularly challenging. Patients are often unable to give a history or are sedated. The clinical features above can be due to the bleed itself or infection at another site. Diagnosis in this setting is usually based on the trajectory of clinical and CSF parameters combined with culture and molecular microbiology results.

Internalized shunt infections present with headache, nausea and altered mental status if drainage is impaired or proximal portion is involved. Fever is absent in up to 80%. Infections predominantly involving distal portion of shunt may present with abdominal (VP) or chest (VPI) pain. Infected VA shunts may present like bacterial endocarditis.

Investigations

If there is a high suspicion of shunt infection or concern for infection with no other source found, CSF should be sent for microscopy and culture, protein and glucose. In those who have received prior antibiotics bacterial 16S PCR can be helpful. In those with suspected VA shunt infection, three sets of blood cultures should be sent.

In up to 20% of internalized shunt infections the CSF white cell count is normal, reflecting infection predominantly consisting of biofilm on the device. The microbiological yield is higher for CSF obtained via shunt-tap than via lumbar puncture.

A single positive culture with a low-grade pathogen e.g., coagulase-negative staphylococci may represent contamination and needs to be interpreted carefully and, if possible, corroborated with a second sample.

Treatment

Empirical therapy usually consists of a third-generation cephalosporin or meropenem but should be guided by local resistance patterns and previous microbiology results in discussion with local infection specialists. For staphylococci resistant to meticillin (flucloxacillin), IV vancomycin is first line. Linezolid is an alternative with good CNS penetration but its use in CNS infections is off-licence.

Removal of the infected shunt is strongly recommended.²

Intra-thecal antimicrobials administered via EVD have not been evaluated in randomized control trials, but many centres have extensive experience in their use. Vancomycin and gentamicin, the most used, are well tolerated. The intra-thecal route is particularly useful for multi-drug-resistant organisms or when the systemic antimicrobial option does not have good CNS penetration.

Community-acquired brain abscess

Brain abscesses occur due to:

- contiguous spread (50%) from ear, mastoid, sinus, teeth, from surgery or trauma
- Haematogenous spread (35%) from the following sources: oral, suppurative lung disease, endocarditis or intra-abdominal. These are often multiple and bilateral.
- No identified source (15%).³

At least 25% of brain abscesses are polymicrobial. Mortality rate is 10%, rising to 50% when ventriculitis is present.

Clinical features

Headache (69%), fever (53%), focal weakness (48%) and seizures (25%) are the main presenting features. Evidence of poor dentition, otitis externa, mastoiditis or murmur can give a clue as to the aetiology.

Investigations

The following are suggested:

- HIV test (this should be routine for all patients with possible CNS infections)
- Blood cultures – three sets if there is suspicion of infective endocarditis
- Imaging – MRI is the modality of choice as it is more sensitive than CT, with diffusion-weighted imaging helping to differentiate from neoplasm.
- Pus sample for bacterial, fungal and mycobacterial culture (plus 16S PCR if culture-negative)
- Serum β -D-glucan and galactomannan If fungal infection is suspected.
- Investigations for source depend on the pathogen and clinical picture but may include orthopantomogram, echocardiography or, if tuberculosis (TB) or *Nocardia* are suspected, a chest X-ray.

Treatment

Surgical: aspiration via burr-hole is the most common procedure for both diagnostic and therapeutic purpose. Indications for consideration of excision include failure of subsequent medical management, thick-walled abscesses, e.g. fungal or *Nocardia*, or traumatic brain abscesses (to remove foreign bodies). If there is suppurative sinus or mastoid disease, then surgical source control is desirable.

Medical: empirical therapy is usually a third-generation cephalosporin and metronidazole. In immunosuppressed patients meropenem may be chosen instead to empirically cover *Nocardia* until culture results.

Subdural abscess/empyema

Subdural abscesses develop between the dura and arachnoid. Most commonly this is secondary to extension of sinus or ear infection through bone but can also occur secondary to suppurative meningitis or, more rarely, as haematogenous seeding onto pre-existing subdural haematoma. Presentation is often acute.

Hospital-associated subdural abscess may occur as a complication of cranial, ear or sinus surgery.

Management is with drainage, either via burr-hole or craniotomy, and antibiotics. The most common regimen is ceftriaxone + metronidazole but may differ as guided by risk factors for resistant organisms and Gram stain and culture of surgical samples.

Spinal infections

Spinal infections (vertebral osteomyelitis, discitis, paraspinal abscesses or a combination) may present on the neurointensive care unit (NICU) post-operatively or because of associated sepsis. Investigations should include imaging, blood cultures and cultures of pus. If abscess is present, drainage should be attempted if feasible. Empirical antibiotics should cover *S. aureus* (>50%), streptococci and Gram-negatives, e.g. *Escherichia coli*. Most infections occur due to haematogenous seeding with a smaller proportion due to contiguous spread from soft tissue infection, psoas muscle infection, rupture of oesophagus or bowel, renal infection or trauma.

Hospital-associated spinal infections occur after spinal surgery or other procedures, e.g. facet joint injections. *S. aureus* is again a common pathogen although others such as *Cutibacterium acnes*, *Pseudomonas* and coagulase negative staphylococci (particularly in the context of spinal metalwork) also need to be considered. Antimicrobial therapy should be adjusted according to culture results.

Spinal tuberculosis and brucellosis should be considered in those with relevant epidemiological, exposure or immunological risk factors.

Encephalitis

Encephalitis may be infectious (direct invasion of brain parenchyma by a pathogen), post-infectious or non-infectious such as primary auto-immune and para-neoplastic. The most common cause of infectious encephalitis in the UK is herpes simplex virus type 1 (HSV1) which will be focussed on here. Table 3 lists notable causes of infectious encephalitis. Septic encephalopathy and malaria can mimic infectious encephalitis.

Clinical features

Most cases of infectious encephalitis present acutely with fever (90% of patients with HSV1 encephalitis have a fever on, or just prior to, admission) and at least one of: focal neurology, seizures, reduced consciousness or change in behaviour.

Notable infectious causes of encephalitis (adapted from British Infection Association encephalitis guideline 2011⁴)

Pathogen	Notes
Viral	
Herpes simplex virus	Most common cause of sporadic encephalitis in UK
Varicella-zoster virus	Usually presents with cerebritis or cerebellitis, or post-infectious vasculopathy.
Enteroviruses	Wide range of nervous system manifestations including encephalitis
Epstein–Barr virus	Usually only seen in immunocompromised individuals
Cytomegalovirus	
Human herpes virus 6 and 7	
Measles	Causes acute post-infectious encephalitis, sub-acute encephalitis and subacute sclerosing panencephalitis
John Cunningham virus	Cause of progressive multi-focal leukoencephalopathy, primarily in immunocompromised
Human immunodeficiency virus	Sub-acute/chronic presentation unless associated with vasculopathy in which case can cause stroke
Tick-borne encephalitis	Majority are associated with travel particularly to Eastern Europe and northern Asia but recent autochthonous infection described in UK
West Nile virus	Associated with travel to North America, Europe, Middle East, Africa, West and Central Asia
Japanese encephalitis	Associated with travel to Asia
Rabies and other lyssaviruses	Zoonotic, most commonly dogs, cats, bats
Bacterial	
Listeria	Predominantly in neonates, older adults and immunocompromised individuals
<i>Mycoplasma pneumoniae</i>	Central nervous system involvement more common in children Also associated with post-infectious neurological phenomena
<i>Treponema pallidum</i> (syphilis)	Dementia-like presentation Can also cause acute, sub-acute or chronic meningitis and other neurological sequelae
<i>Borrelia burgdorferi</i> (Lyme disease)	Rarely causes encephalomyelitis
Rickettsiae	Travel associated
Fungal	
<i>Cryptococcus neoformans</i>	Often a sub-acute presentation
Parasitic	
Amoeba, e.g. <i>Naegleria fowleri</i>	Rare but can be rapidly progressive and devastating. Associated with fresh-water swimming
Prions	
Sporadic, inherited or acquired forms	Sub-acute or chronic presentation

Table 3**Investigations**

CSF PCR in HSV1 encephalitis may be negative in first few days of illness. In suspected cases CSF should be repeated 3–7 days later.

MRI on day 3–4 of illness is highly sensitive for HSV encephalitis, typical features including asymmetrical involvement of the temporal and frontal lobes and insular cortex. Immunosuppressed individuals may display atypical imaging features.

Treatment

High-dose intravenous aciclovir should be started promptly if viral encephalitis is suspected. Even if initial CSF HSV PCR is negative, aciclovir should be continued if the history and imaging are compatible and CSF should be repeated. Results of a randomised control trial assessing the impact of adjuvant steroids in HSV encephalitis are awaited.

Infectious causes of stroke

Several infections have the potential to cause ischaemic stroke (See Table 4). In addition, infection can be associated with haemorrhagic stroke or sub-arachnoid haemorrhage. A rapidly developing aneurysm should raise the suspicion of mycotic aneurysm.

Central nervous system tuberculosis

Clinical presentation with CNS TB is typically insidious but can be acute. TB may cause meningitis, cerebral tuberculomas, spondylodiscitis, spinal arachnoiditis, paraspinal abscesses, transverse myelitis or a combination of these. Mycobacterial culture of CSF (large volume), tissue or pus are the key microbiological investigations. Gene Xpert is a rapid molecular test that, whilst not marketed for these samples, is widely used and can be helpful with making a rapid diagnosis. Treatment is with a combination of anti-mycobacterial agents. Adjuvant steroids are always used in meningitis⁵ and often in the other CNS manifestations. Up to one-third of patients experience paradoxical worsening of disease in the first few months of treatment and may require intensification of the anti-inflammatory component of treatment.

Penicillin allergy

β-lactams remain the most effective and appropriate antibiotics for many infections encountered on neurocritical care. Given the already limited choice of antibacterials with good penetration

Infective causes of ischaemic stroke

Cause	Specific tests required
Infective endocarditis (suspect in any patient presenting with history of fever followed by stroke or in those with multi-territory infarcts)	At least three sets of blood cultures (before antibiotics if possible) Echocardiogram
Syphilis (<i>Treponema pallidum</i> subsp. <i>pallidum</i>)	Syphilis serology (blood) If positive needs CSF studies including paired serology on CSF and serum CSF VZV PCR If PCR negative but still clinical suspicion, intra-thecal antibody testing Viral swab of any vesicles if present on skin
Varicella-zoster virus (VZV)	Serum + CSF cryptococcal antigen Serum β -D-glucan and galactomannan Large volume (5 ml) CSF for fungal culture Large volume (5 ml) CSF for mycobacterial culture
Fungal meningitis	HIV serology Viral swab of nose/throat for PCR Lyme disease serology
Tuberculous meningitis	
HIV-associated vasculopathy	
SARS-CoV-2 (COVID-19)	
Lyme disease (<i>Borrelia burgdorferi</i>)	

COVID-19, coronavirus disease; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome co-virus 2.

Table 4

into the CNS, the importance of clarifying a penicillin ‘allergy’ history holds even more importance in this setting.

Data show that less than 5% of those with a penicillin allergy have a true allergy when tested and that only 1–2% of those with true penicillin allergy develop a reaction with cephalosporins.⁶

Other infections in the immunocompromised

A significant proportion of patients on NICU are immunocompromised, either through underlying disease or as a side effect of treatment. These patients are at risk of re-activation of ‘latent’ infections, e.g. TB or *Strongyloides*,⁷ and active disease caused by organisms that were previously just colonizing, e.g. *Aspergillus* or *Pneumocystis jirovecii*. Patients who are planned for immunosuppression, including corticosteroids alone, should undergo risk assessment, testing and, where appropriate, treatment and vaccination.⁸ ◆

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